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L4           30 SEA ABB=ON  PLU=ON  L3 AND NOC3/ES
L5            6 SEA ABB=ON  PLU=ON  L4 AND NR=3
L6            2 SEA ABB=ON  PLU=ON  L5 AND C21 H22 BR N3 O4/MF
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L7              STR 744198-15-0
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L10           6 SEA FAM FUL L9

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L11           7 SEA ABB=ON  PLU=ON  L10

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L15            0 SEA ABB=ON  PLU=ON  L14 AND BABSAN/FA

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L18            0 SEA ABB=ON  PLU=ON  L17 NOT L11

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                CHAITAN SHIVKUMAR"/AU OR "KHOSLA CHAITIN"/AU OR "KHOSLA
                CHAITON"/AU)
                E CHOI K/AU
L20         4095 SEA ABB=ON  PLU=ON  CHOI K?/AU
L21            5 SEA ABB=ON  PLU=ON  L19 AND L20

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                E E3+ALL
L22         2522 SEA ABB=ON  PLU=ON  "CELIAC DISEASE"+PFT/CT
                E DERMATITIS HERPETIFORMIS/CT
                E E3+ALL
L23          207 SEA ABB=ON  PLU=ON  "DERMATITIS (L) HERPETIFORMIS"+PFT/CT
L24          373 SEA ABB=ON  PLU=ON  (CELIAC SPRUE? OR DERMATITIS HERPET?)/OBI,B
                I
L25            2 SEA ABB=ON  PLU=ON  L11 AND (L22 OR L23 OR L24)
L26            7 SEA ABB=ON  PLU=ON  (L11 OR L25)
L27            7 SEA ABB=ON  PLU=ON  (L1 OR L26)

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FILE LAST UPDATED: 18 Jul 2006  (20060718/ED)

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                 OR "KHOSLA CHAITAN SHIVKUMAR"/AU OR "KHOSLA CHAITIN"/AU OR
                 "KHOSLA CHAITON"/AU)
L20         4095 SEA FILE=CAPLUS ABB=ON  PLU=ON  CHOI K?/AU
L21            5 SEA FILE=CAPLUS ABB=ON  PLU=ON  L19 AND L20


=> d ibib abs l21 tot

L21  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:362104  CAPLUS
DOCUMENT NUMBER:          144:404112
TITLE:                    Pharmacologic transglutaminase inhibition attenuates
                          drug-primed liver hypertrophy but not Mallory body
                          formation
AUTHOR(S):                Strnad, Pavel; Siegel, Matthew; Toivola, Diana M.;
                          Choi, Kihang; Kosek, Jon C.; Khosla,
                          Chaitan; Omary, M. Bishr
CORPORATE SOURCE:         Department of Medicine, Palo Alto VA Medical Center,
                          Palo Alto, CA, 94304, USA
SOURCE:                   FEBS Letters (2006), 580(9), 2351-2357
                          CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Mallory bodies (MBs) are characteristic of several liver disorders, and
     consist primarily of keratins with transglutaminase-generated keratin
     crosslinks. We tested the effect of the transglutaminase-2 (TG2)
     inhibitor KCC009 on MB formation in a mouse model fed 3,5-diethoxycarbonyl-
     1,4-dihydrocollidine (DDC). KCC009 decreased DDC-induced liver
     enlargement without affecting MB formation or extent of liver injury. TG2
     protein and activity increased after DDC feeding and localized within and
     outside hepatocytes. KCC009 inhibited DDC-induced hepatomegaly by
     affecting hepatocyte cell size rather than proliferation. Hence, TG2 is a
     potential mediator of injury-induced hepatomegaly via modulation of
     hepatocyte hypertrophy, and KCC009-mediated TG2 inhibition does not affect
     mouse MB formation.
REFERENCE COUNT:          34    THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:217140  CAPLUS
DOCUMENT NUMBER:          144:293068
TITLE:                    Preparation of dihydroisoxazole and isatin derivatives
                          for use in pharmaceutical compositions as
                          transglutaminase inhibitors
INVENTOR(S):              Khosla, Chaitan; Watts, Richard Edward;
                          Siegel, Matthew John; Pinkas, Daniel M.; Choi,
                          Kihang; Rich, Keith M.
PATENT ASSIGNEE(S):       The Board of Trustees of the Leland Stanford Junior
                          University, USA
SOURCE:                   U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of U.S.
                          Ser. No. 716,846.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
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PATENT INFORMATION:

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US 2006052308	A1	20060309	US 2005-213173	20050826
US 2004167069	A1	20040826	US 2003-716846	20031118
PRIORITY APPLN. INFO.:			US 2003-716846	A2 20031118
			US 2002-380761P	P 20020514 → Earliest PPD
			US 2002-392782P	P 20020628
			US 2002-422933P	P 20021031
			US 2002-428033P	P 20021120
			WO 2003-US15343	A2 20030514

OTHER SOURCE(S): MARPAT 144:293068

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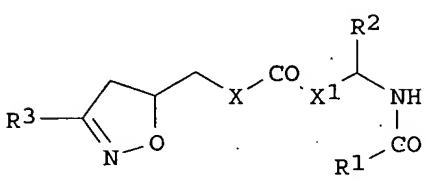

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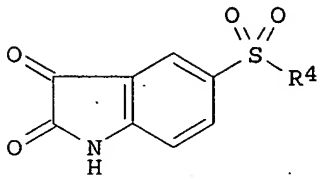

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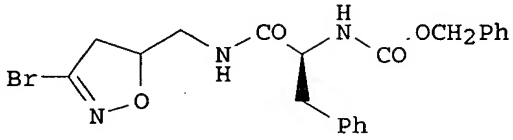

III

AB Transglutaminase (tTGase) inhibitors, such as I [R1, R2 = H, alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkoxy, alkylthio, halogen, etc.; R3 = Cl, Br; X = NH, O; X1 = (CH2)n, n = 0-10] and II [R4 = alkylamino, benzylamino, amino acid residue, etc.], were prepared for therapeutic use in the treatment of neurol. cancers. Thus, dihydroisoxazole phenylalanine derivative III was prepared with 52% yield by an amidation reaction of 3-bromo-5-aminomethyl-4,5-dihydroisoxazole with N-(benzyloxycarbonyl)-L-phenylalanine using HOBt in DMF. The prepared dihydroisoxazoles, isatins and peptides were tested for tTGase-2 inhibitory activity and for inhibition of astrocytoma, glioblastoma, and meningioma tumors.

L21 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2005:1064565 CAPLUS
DOCUMENT NUMBER:	144:246627
TITLE:	Tissue transglutaminase 2 inhibition promotes cell death and chemosensitivity in glioblastomas
AUTHOR(S):	Yuan, Liya; Choi, Kihang; Khosla, Chaitan; Zheng, Xiao; Higashikubo, Ryuji; Chicoine, Michael R.; Rich, Keith M.
CORPORATE SOURCE:	Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO, USA
SOURCE:	Molecular Cancer Therapeutics (2005), 4(9), 1293-1302 CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER:	American Association for Cancer Research

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tissue transglutaminase 2 belongs to a family of transglutaminase proteins that confers mech. resistance from proteolysis and stabilizes proteins. Transglutaminase 2 promotes transamidation between glutamine and lysine residues with the formation of covalent linkages between proteins. Transglutaminase 2 also interacts and forms complexes with proteins important in extracellular matrix organization and cellular adhesion. We have identified the novel finding that treatment of glioblastoma cells with transglutaminase 2 inhibitors promotes cell death and enhances sensitivity to chemotherapy. Treatment with either the competitive transglutaminase 2 inhibitor, monodansylcadaverine, or with highly specific small-mol. transglutaminase 2 inhibitors, KCA075 or KCC009, results in induction of apoptosis in glioblastoma cells. Treatment with these transglutaminase 2 inhibitors resulted in markedly decreased levels of the prosurvival protein, phosphorylated Akt, and its downstream targets. These changes promote a proapoptotic profile with altered levels of multiple intracellular proteins that determine cell survival. These changes include decreased levels of the antiapoptotic proteins, survivin, phosphorylated Bad, and phosphorylated glycogen synthetase kinase 3β (GSK-3β), and increased levels of the proapoptotic BH3-only protein, Bim. In vivo studies with s.c. murine DBT glioblastoma tumors treated with transglutaminase 2 inhibitors combined with the chemotherapeutic agent, N-N'-bis (2-chloroethyl)-N-nitrosourea (BCNU), decreased tumor size based on weight by 50% compared with those treated with BCNU alone. Groups treated with transglutaminase 2 inhibitors showed an increased incidence of apoptosis determined with deoxynucleotidyl transferase-mediated biotin nick-end labeling staining. These studies identify inhibition of transglutaminase 2 as a potential target to enhance cell death and chemosensitivity in glioblastomas.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:356173 CAPLUS
DOCUMENT NUMBER: 143:125809
TITLE: Chemistry and Biology of Dihydroisoxazole Derivatives: Selective Inhibitors of Human Transglutaminase 2
AUTHOR(S): Choi, Kihang; Siegel, Matthew; Piper, Justin L.; Yuan, Liya; Cho, Eun; Strnad, Pavel; Omary, Bishr; Rich, Keith M.; Khosla, Chaitan
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (2005), 12(4), 469-475
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Summary: 3-Halo-4,5-dihydroisoxazoles are attractive warheads for the selective inhibition of nucleophilic active sites in biol. systems. A series of 3-bromo-4,5-dihydroisoxazole compds. were prepared and tested for their ability to irreversibly inhibit human transglutaminase 2 (TG2), an enzyme that plays an important role in the pathogenesis of diverse disorders including Celiac Sprue and certain types of cancers. Several compds. showed high specificity for human TG2 (kinh/KI > 2000 min-1M-1) but essentially no reactivity (k < 1 min-1M-1) toward physiol. thiols such as glutathione. The pharmacokinetic and pharmacodynamic properties of a prototype dihydroisoxazole inhibitor, 1b, were evaluated; in mice the compound showed good oral bioavailability, short serum half-life and

efficient TG2 inhibition in small intestinal tissue, and low toxicity. It also showed excellent synergism with N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU, carmustine) against refractory glioblastoma tumors in mice. A fluorescent dihydroisoxazole inhibitor 5 facilitated microscopic visualization of TG2 endocytosis from the extracellular surface of HCT-116 cells. Together, these findings demonstrate the promise of dihydroisoxazole compds. as probes for the biol. of TG2 and its role in human disease.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:703116 CAPLUS
DOCUMENT NUMBER: 141:218994
TITLE: Tissue transglutaminase (tTGase) inhibitor therapy for celiac sprue and dermatitis herpetiformis
INVENTOR(S): Khosla, Chaitan; Choi, Kihang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of Appl. No. PCT/US03/15343.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167069	A1	20040826	US 2003-716846	20031118
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			WO 2003-US15343	A2	20030514
			WO 2003-US15506	W	20030514
			US 2003-716846	A	20031118
			WO 2003-US37434	W	20031120

OTHER SOURCE(S): MARPAT 141:218994

AB Administering an ED of a tTGase inhibitor to a celiac sprue or dermatitis herpetiformis patient reduces the toxic effects of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten. Preparation and tissue transglutaminase-inhibiting activity of dihydroisoxazole moiety-containing compds. is included.

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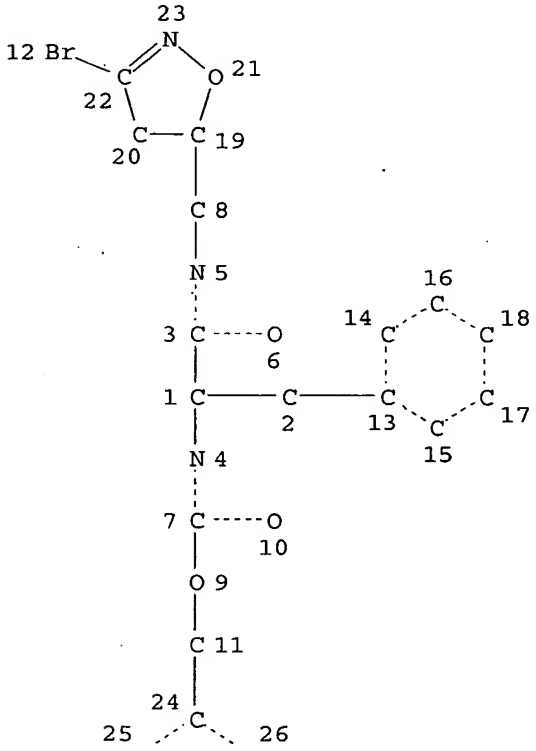

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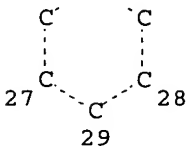

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STEREO ATTRIBUTES: NONE
L10           6 SEA FILE=REGISTRY FAM FUL L9
L11           7 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10
L22        2522 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CELIAC DISEASE"+PFT/CT
L23         207 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DERMATITIS (L) HERPETIFORMIS"
                +PFT/CT
L24         373 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (CELIAC SPRUE? OR DERMATITIS
                HERPET?)/OBI,BI
L25           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND (L22 OR L23 OR L24)
L26           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L11 OR L25)
L27           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L1 OR L26)


=> d ibib abs hitstr l27 tot

L27  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:217140  HCAPLUS
DOCUMENT NUMBER:          144:293068
TITLE:                    Preparation of dihydroisoxazole and isatin derivatives
                          for use in pharmaceutical compositions as
                          transglutaminase inhibitors
INVENTOR(S):              Khosla, Chaitan; Watts, Richard Edward; Siegel,
                          Matthew John; Pinkas, Daniel M.; Choi, Kihang; Rich,
                          Keith M.
PATENT ASSIGNEE(S):       The Board of Trustees of the Leland Stanford Junior
                          University, USA
SOURCE:                   U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of U.S.
                          Ser. No. 716,846.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     US 2006052308         A1    20060309    US 2005-213173           20050826 <--
     US 2004167069         A1    20040826    US 2003-716846           20031118 <--
PRIORITY APPLN. INFO.:                       US 2003-716846       A2  20031118 <--
                                             US 2002-380761P      P   20020514
                                             US 2002-392782P      P   20020628
                                             US 2002-422933P      P   20021031
                                             US 2002-428033P      P   20021120
                                             WO 2003-US15343      A2  20030514
OTHER SOURCE(S):          MARPAT 144:293068
GI
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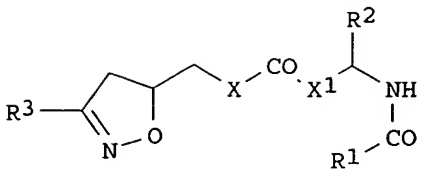

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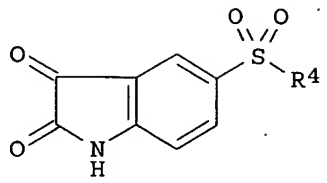

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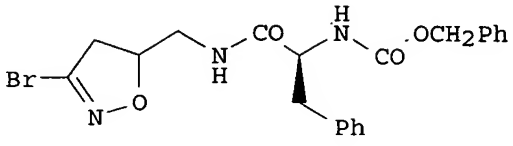


III

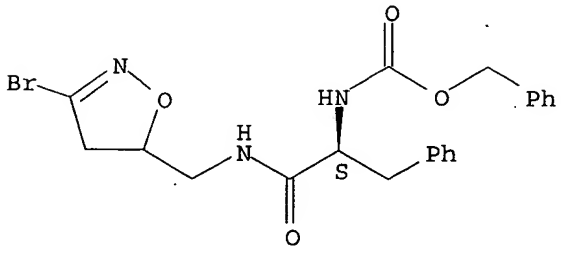
AB Transglutaminase (tTGase) inhibitors, such as I [R1, R2 = H, alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkoxy, alkylthio, halogen, etc.; R3 = Cl, Br; X = NH, O; X1 = (CH2)n, n = 0-10] and II [R4 = alkylamino, benzylamino, amino acid residue, etc.], were prepared for therapeutic use in the treatment of neurol. cancers. Thus, dihydroisoxazole phenylalanine derivative III was prepared with 52% yield by an amidation reaction of 3-bromo-5-aminomethyl-4,5-dihydroisoxazole with N-(benzyloxycarbonyl)-L-phenylalanine using HOBt in DMF. The prepared dihydroisoxazoles, isatins and peptides were tested for tTGase-2 inhibitory activity and for inhibition of astrocytoma, glioblastoma, and meningioma tumors.

IT 744198-09-2P 744198-15-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dihydroisoxazole and isatin derivs. for use in pharmaceutical compns. as transglutaminase-2 inhibitors)

RN 744198-09-2 HCAPLUS

CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

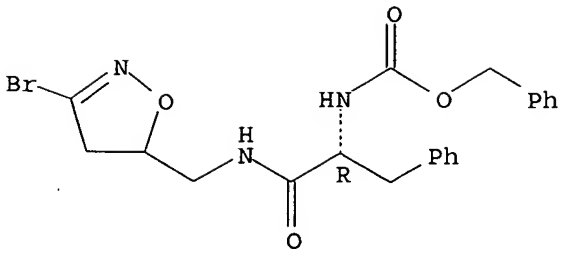
Absolute stereochemistry.



RN 744198-15-0 HCAPLUS

CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

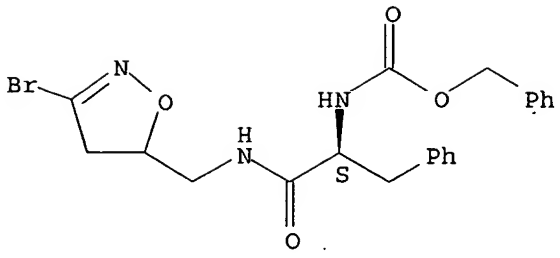


L27 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:356173 HCAPLUS
DOCUMENT NUMBER: 143:125809
TITLE: Chemistry and Biology of Dihydroisoxazole Derivatives: Selective Inhibitors of Human Transglutaminase 2
AUTHOR(S): Choi, Kihang; Siegel, Matthew; Piper, Justin L.; Yuan, Liya; Cho, Eun; Strnad, Pavel; Omary, Bishr; Rich, Keith M.; Khosla, Chaitan
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305, USA
SOURCE: Chemistry & Biology (2005), 12(4), 469-475
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Summary: 3-Halo-4,5-dihydroisoxazoles are attractive warheads for the selective inhibition of nucleophilic active sites in biol. systems. A series of 3-bromo-4,5-dihydroisoxazole compds. were prepared and tested for their ability to irreversibly inhibit human transglutaminase 2 (TG2), an enzyme that plays an important role in the pathogenesis of diverse disorders including Celiac Sprue and certain types of cancers. Several compds. showed high specificity for human TG2 (kinh/KI > 2000 min-1M-1) but essentially no reactivity (k < 1 min-1M-1) toward physiol. thiols such as glutathione. The pharmacokinetic and pharmacodynamic properties of a prototype dihydroisoxazole inhibitor, 1b, were evaluated; in mice the compound showed good oral bioavailability, short serum half-life and efficient TG2 inhibition in small intestinal tissue, and low toxicity. It also showed excellent synergism with N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU, carmustine) against refractory glioblastoma tumors in mice. A fluorescent dihydroisoxazole inhibitor 5 facilitated microscopic visualization of TG2 endocytosis from the extracellular surface of HCT-116 cells. Together, these findings demonstrate the promise of dihydroisoxazole compds. as probes for the biol. of TG2 and its role in human disease.

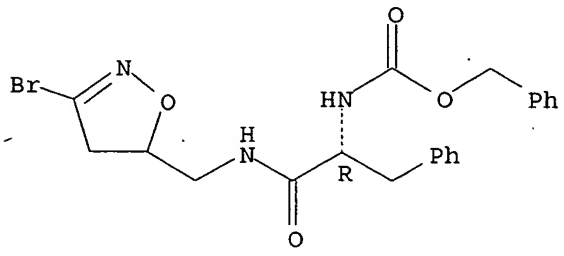
IT 744198-09-2 744198-15-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroisoxazole derivs. as inhibitors of human transglutaminase)
RN 744198-09-2 HCAPLUS
CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 744198-15-0 HCAPLUS
CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:703116 HCAPLUS
DOCUMENT NUMBER: 141:218994
TITLE: Tissue transglutaminase (tTGase) inhibitor therapy for celiac sprue and dermatitis herpetiformis
INVENTOR(S): Khosla, Chaitan; Choi, Kihang
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of Appl. No. PCT/US03/15343.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167069	A1	20040826	US 2003-716846	20031118 <--
CA 2487247	AA	20031127	CA 2003-2487247	20030514
WO 2003096979	A2	20031127	WO 2003-US15343	20030514
WO 2003096979	A3	20040212		

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WO 2003096984 A2 20031127 WO 2003-US15506 20030514

WO 2003096984 A3 20040701

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AU 2003234597 A1 20031202 AU 2003-234597 20030514

AU 2003234634 A1 20031202 AU 2003-234634 20030514

EP 1507549 A2 20050223 EP 2003-728939 20030514

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CA 2502700 AA 20040603 CA 2003-2502700 20031120

WO 2004045392 A2 20040603 WO 2003-US37434 20031120

WO 2004045392 A3 20040826

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AU 2003294473 A1 20040615 AU 2003-294473 20031120

EP 1563300 A2 20050817 EP 2003-789958 20031120

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WO 2005049064 A1 20050602 WO 2004-US37873 20041112 <--

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005256054 A1 20051117 US 2005-514005 20050513

US 2006035838 A1 20060216 US 2005-514177 20050628

US 2006052308 A1 20060309 US 2005-213173 20050826 <--

PRIORITY APPLN. INFO.: US 2002-380761P P 20020514 APP

US 2002-392782P P 20020628

US 2002-422933P P 20021031

US 2002-428033P P 20021120

WO 2003-US15343 A2 20030514

WO 2003-US15506 W 20030514

US 2003-716846 A 20031118 <--
WO 2003-US37434 W 20031120

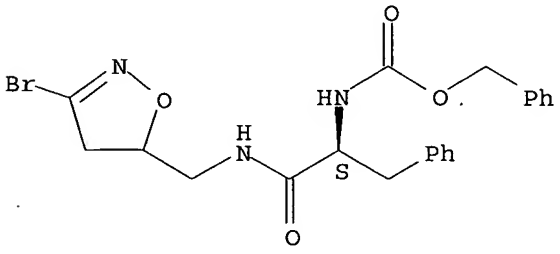
OTHER SOURCE(S): MARPAT 141:218994

AB Administering an ED of a tTGase inhibitor to a celiac sprue or dermatitis herpetiformis patient reduces the toxic effects of toxic gluten oligopeptides, thereby attenuating or eliminating the damaging effects of gluten. Preparation and tissue transglutaminase-inhibiting activity of dihydroisoxazole moiety-containing compds. is included.

IT 744198-09-2P 744198-15-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tissue transglutaminase inhibitor therapy for celiac sprue and dermatitis herpetiformis)

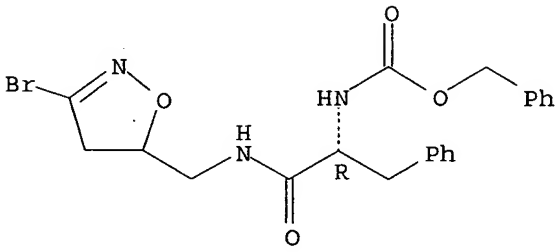
RN 744198-09-2 HCAPLUS
CN Carbamic acid, [(1S)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 744198-15-0 HCAPLUS
CN Carbamic acid, [(1R)-2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



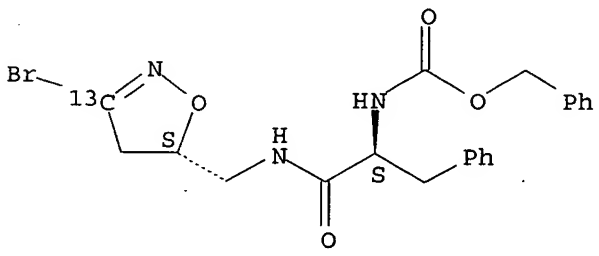
L27 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:444144 HCAPLUS
DOCUMENT NUMBER: 119:44144
TITLE: Solid-state carbon-13 NMR study of a transglutaminase-inhibitor adduct
AUTHOR(S): Auger, Michele; McDermott, Ann E.; Robinson, Valerie; Castelhano, Arlindo L.; Billedeau, Roland J.; Pliura, Diana H.; Krantz, Allen; Griffin, Robert G.
CORPORATE SOURCE: Francis Bitter Natl. Magnet Lab., Massachusetts Inst.

Technol., Cambridge, MA, 02139, USA
SOURCE: Biochemistry (1993), 32(15), 3930-4
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Solid-state 13C NMR was used to study the structure of the adduct resulting from the inactivation of transglutaminase by 3-halo-4,5-dihydroisoxazoles. These inhibitors were conceived on the assumption that they would inhibit transglutaminase by attack of an enzyme active site cysteine SH group on the imine C atom of the dihydroisoxazole ring. The tetrahedral intermediate formed could then break down with the loss of the halide group and the subsequent formation of a stable imino thioether adduct. The 13C CPMAS NMR spectra of the chloro-, bromo-, and (ethylthio)dihydroisoxazole inhibitors were compared, and the results indicated that the chemical shift of the C-3 atom is sensitive to the nature of the heteroatom. Subtraction of the natural-abundance 13C solid-state NMR spectrum of the enzyme from that of the enzyme inactivated by C-3-labeled chlorodihydroisoxazole revealed a broad peak at 156 ppm. The chemical shift of this peak was very close to that observed for a model 3-ethylthio compound and suggested the formation of a stable imino thioether enzyme adduct. Similar results were obtained for lyophilized enzyme adducts and for frozen solns. of the enzyme adduct in the absence and presence of Ca2+. These results were compared with those obtained by solution NMR on an aqueous solution of the enzyme-inhibitor complex. The 13C-labeled C-3 resonance was not observed in this case.

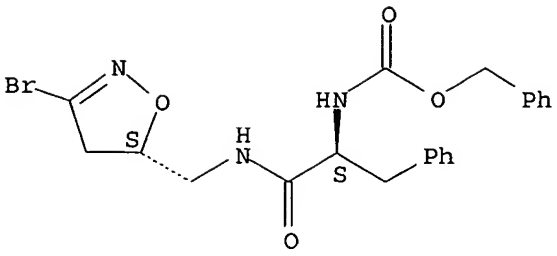
IT 148416-83-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 148416-83-5 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl-3-13C)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



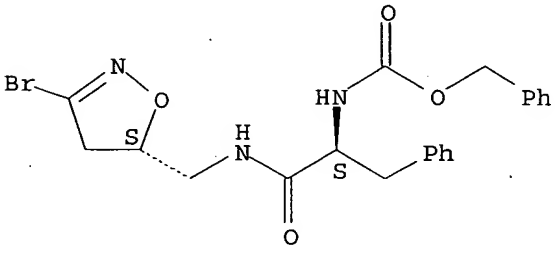
IT 120244-83-9 120244-83-9D, transglutaminase adducts
RL: PRP (Properties)
(structure of, solid-state carbon-13 NMR study of)
RN 120244-83-9 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 120244-83-9 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L27 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:557401 HCAPLUS
DOCUMENT NUMBER: 117:157401
TITLE: Transglutaminase inhibitors as hair growth inhibitors
INVENTOR(S): Handelman, Joseph H.; Shander, Douglas; Funkhouser, Margaret G.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9211007	A1	19920709	WO 1991-US9645	19911219
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
→ US 5143925	A	19920901	US 1991-794321	19911112
CA 2098102	AA	19920620	CA 1991-2098102	19911219
CA 2098102	C	19961105		
AU 9191653	A1	19920722	AU 1991-91653	19911219
AU 656550	B2	19950209		
EP 563301	A1	19931006	EP 1992-903695	19911219
EP 563301	B1	20000510		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				

other use?

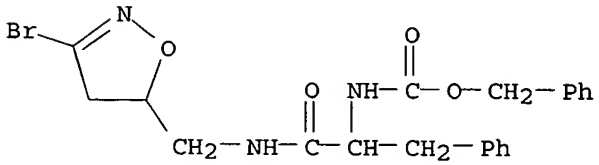
JP 06504057	T2	19940512	JP 1991-503400	19911219
AT 192644	E	20000515	AT 1992-903695	19911219
ES 2145005	T3	20000701	ES 1992-903695	19911219
PRIORITY APPLN. INFO.:			US 1990-632126	A1 19901220
			WO 1991-US9645	A 19911219

AB The rate and character of mammalian hair growth is altered by topical application to the skin of a composition containing an inhibitor of the transglutaminase. A topical composition contained 5-(N-benzyloxycarbonyl-L-phenylalaninamido-methyl)-3-bromo-4,5-dihydroisoxazole 20, acetone 75, propylene carbonate 20, benzyl alc. 5%. The application of above composition on hamster skin for 18 days inhibited the hair mass by 87.87%.

IT 115329-49-2
RL: BIOL (Biological study)
(as hair growth inhibitor, topical composition containing)

RN 115329-49-2 HCAPLUS

CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



L27 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1989:193339 HCAPLUS
DOCUMENT NUMBER:	110:193339
TITLE:	Synthesis, chemistry, and absolute configuration of novel transglutaminase inhibitors containing a 3-halo-4,5-dihydroisoxazole
AUTHOR(S):	Castelhano, Arlindo L.; Billedeau, Roland; Pliura, Diana H.; Bonaventura, Bonnie J.; Krantz, Allen
CORPORATE SOURCE:	Syntex Inc., Mississauga, ON, L5N 3X4, Can.
SOURCE:	Bioorganic Chemistry (1988), 16(3), 335-40 CODEN: BOCMBM; ISSN: 0045-2068
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 110:193339

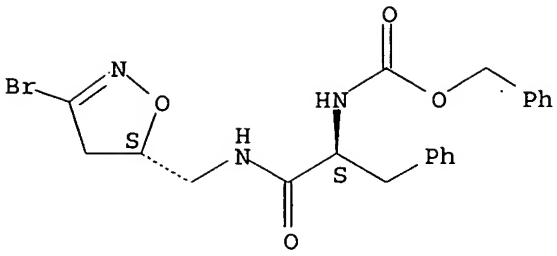
AB The preparation of potent transglutaminase inhibitors containing a 3-halo-4,5-dihydroisoxazole and the determination of their absolute configuration are described. Interestingly, reaction of halodihydroisoxazoles with thiolate is dependent on the nature of the halogen atom, with the bromide primarily undergoing ring cleavage and the chloride undergoing displacement with the ring intact. This result may have implications as regards mechanisms of transglutaminase inhibition by 3-halo-4,5-dihydroisoxazoles.

IT 120244-83-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(inactivation by, of transglutaminase)

RN 120244-83-9 HCAPLUS

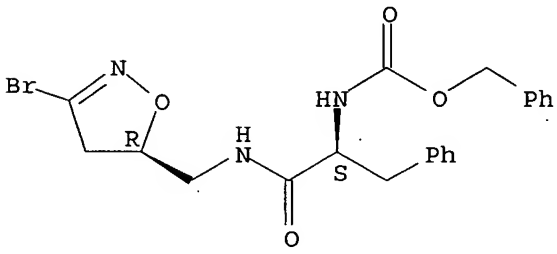
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 120245-03-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 120245-03-6 HCAPLUS
CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L27 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:76070 HCAPLUS
DOCUMENT NUMBER: 110:76070
TITLE: Preparation and testing of amino acid amides of 5-(aminomethyl)-4,5-dihydroisoxazoles as transglutaminase inhibitors
INVENTOR(S): Castelhano, Arlindo L.; Krantz, Alexander; Pliura, Diana H.; Venuti, Michael C.; De Young, Lawrence M.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: Eur. Pat. Appl., 95 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 237082	A2	19870916	EP 1987-103700	19870313
EP 237082	A3	19880914		
EP 237082	B1	19910529		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DK 8701303	A	19870915	DK 1987-1303	19870313
AU 8769987	A1	19870917	AU 1987-69987	19870313
AU 599636	B2	19900726		

JP 62252779	A2	19871104	JP 1987-59922		19870313
HU 44244	A2	19880229	HU 1987-1105		19870313
HU 201032	B	19900928			
ZA 8701860	A	19881026	ZA 1987-1860		19870313
US 4912120	A	19900327	US 1987-25451		19870313
IL 81887	A1	19910512	IL 1987-81887		19870313
IL 95264	A1	19910512	IL 1987-95264		19870313
AT 63906	E	19910615	AT 1987-103700		19870313
ES 2038609	T3	19930801	ES 1987-103700		19870313
US 4929630	A	19900529	US 1989-404791		19890908
PRIORITY APPLN. INFO.:			US 1986-839743	A	19860314
			EP 1987-103700	A	19870313
			IL 1987-81887	A	19870313
			US 1987-25451	A3	19870313

OTHER SOURCE(S): CASREACT 110:76070; MARPAT 110:76070

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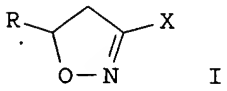


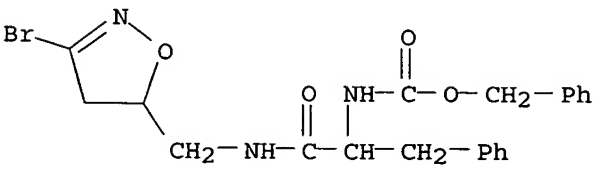
I

AB The title compds. [I; R = R1R2NCHR3CONHCH2, R2 = NHCH2; NR1R2 = phthalimido; R1R3 = (CH2)3, CH2CH(OH)CH2; R1 = H, Me; R2 = H, alkyl, lower alkylsulfonyl, (lower alkyl)arylsulfonyl, 9-fluorenylmethyloxycarbonyl, succinyl, cinnamoyl, CHO, alkanoyl, amino acid residue, etc.; R3 = H, lower alkyl, CHMeOCH2Ph, CH2CONH2, (CH2)2NH2, (CH2)4NHCO2CMe3, (CH2)2CH(OH)CH2NH2, (un)substituted phenylalkyl, etc.; X = halo, OR4, SR4, S(O)R4, SO2R4, SO2NH2, SO2NHR4; R4 = lower alkyl, fluorinated C2-3 alkyl, (un)substituted aryl, (un)substituted NH2, 1H-imidazol-1-yl] (II), useful as transglutaminase inhibitors, were prepared To a solution of 700 mg N-benzyloxycarbonyl-L-phenylalanine allyl amide in EtOAc/H2O was added NaHCO3 and in small portions 631 mg dibromoformaldoxime. The progress of the reaction was monitored by thin layer chromatog. and after completion of the reaction (2-4 h) the mixture was worked up to give I (R = CBZ-Phe, X = Br) (IV). A gel consisting of IV, 2.5% Klurel, 10% diisopropyl adipate, 80% EtOH and 5% polyethylene glycol was applied once daily to two dogs for 14 days, resulting in clearing of majority of blackhead-like lesions as well as many whitehead-like lesions. A gel formulation containing 1 IV, 3 H2O, 2 Carbopol, 0.01 Pr gallate, and 0.01% edetate disodium in 100 mL propylene glycol was given.

IT 115329-49-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as transglutaminase inhibitor)

RN 115329-49-2 HCAPLUS

CN Carbamic acid, [2-[[(3-bromo-4,5-dihydro-5-isoxazolyl)methyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



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FILE 'BEILSTEIN' ENTERED AT 13:50:08 ON 19 JUL 2006
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FILE LAST UPDATED ON JUNE 16, 2006

FILE COVERS 1771 TO 2006.
*** FILE CONTAINS  9,606,495 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
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   Reaction data for BEILSTEIN compounds may be displayed
   immediately with the display codes PRE (preparations) and REA
   (reactions).  A substance answer set retrieved after the search
   for a chemical name, a compounds with available reaction
   information by combining with PRE/FA, REA/FA or more generally
   with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
   between a BEILSTEIN compound and belonging reactions. For mo
   detailed reaction searches BRNs can be searched as reaction
   partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

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  ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
  COMPOUND AT A GLANCE.

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L9              STR
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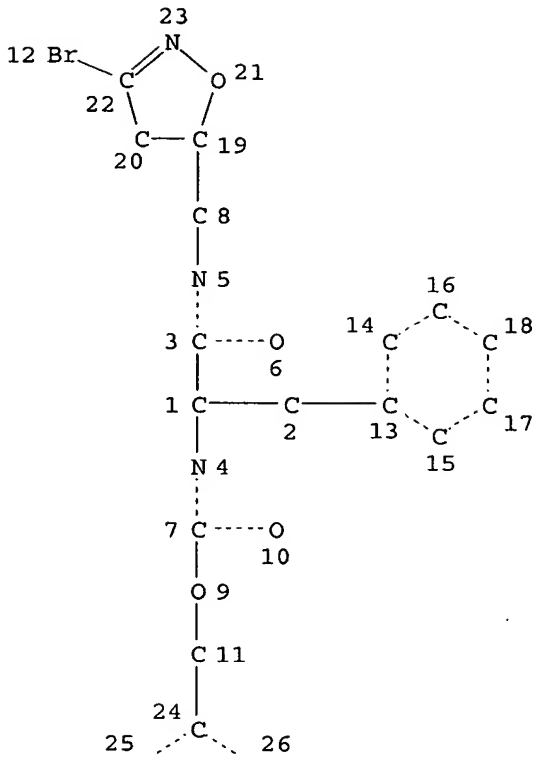
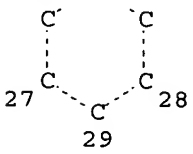


Page 1-A



Page 2-A
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
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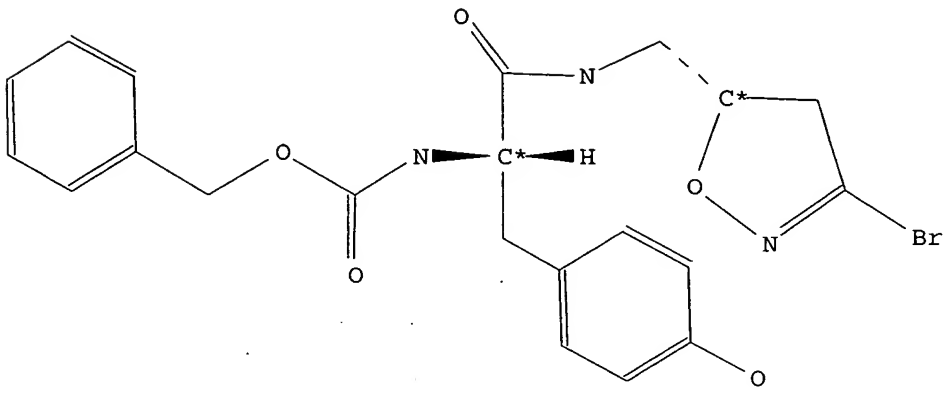
L13 ANSWER 1 OF 2 BEILSTEIN COPYRIGHT 2006 BEILSTEIN MDL on STN

Beilstein Records (BRN): 5386200
CAS Reg. No. (RN): 115329-50-5, 120244-89-5, 120244-90-8
Chemical Name (CN): <1-<(3-bromo-4,5-dihydro-isoxazol-5-ylmethyl)-carbamoyl>-2-(4-hydroxy-phenyl)-

Same as 2/2

Saloni Sharma 07/19/2006

Autonom Name (AUN):	ethyl>-carbamic acid benzyl ester <1-<(3-bromo-4,5-dihydro-isoxazol-5-ylmethyl)-carbamoyl>-2-(4-hydroxy-phenyl)-ethyl>-carbamic acid benzyl ester
Molec. Formula (MF):	C21 H22 Br N3 O5
Molecular Weight (MW):	476.33
Lawson Number (LN):	31551, 16193, 5228, 1762
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	4730068
Tautomer ID (TAUTID):	5126818
Beilstein Citation (BSO):	6-27
Entry Date (DED):	1993/05/04
Update Date (DUPD):	1994/02/18



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FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

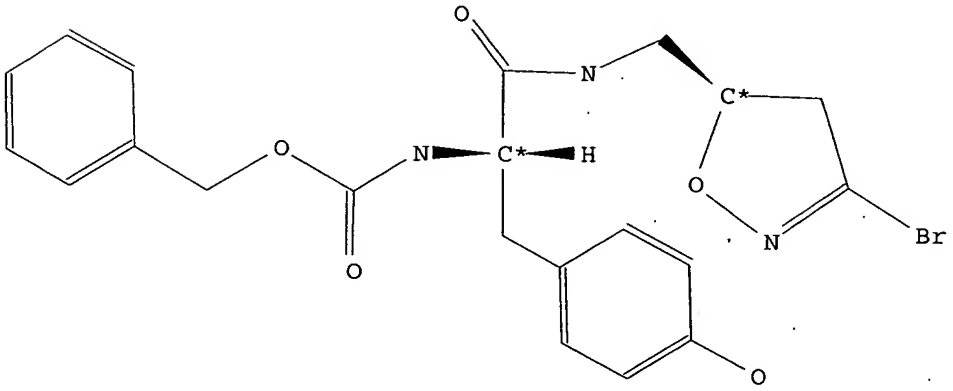
Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Rohloff, John C.; Robinson, James III; Gardner, John O., Tetrahedron Lett., CODEN: TELEAY, 33(22), <1992>, 3113-3116; BABS-5654059

L13 ANSWER 2 OF 2 BEILSTEIN COPYRIGHT 2006 BEILSTEIN MDL on STN

Beilstein Records (BRN):	5386199
CAS Reg. No. (RN):	115329-50-5, 120244-89-5, 120244-90-8
Chemical Name (CN):	<1-<(3-bromo-4,5-dihydro-isoxazol-5-ylmethyl)-carbamoyl>-2-(4-hydroxy-phenyl)-ethyl>-carbamic acid benzyl ester
Autonom Name (AUN):	<1-<(3-bromo-4,5-dihydro-isoxazol-5-ylmethyl)-carbamoyl>-2-(4-hydroxy-phenyl)-ethyl>-carbamic acid benzyl ester
Molec. Formula (MF):	C21 H22 Br N3 O5
Molecular Weight (MW):	476.33
Lawson Number (LN):	31551, 16193, 5228, 1762
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	4730068
Tautomer ID (TAUTID):	5126818
Beilstein Citation (BSO):	6-27
Entry Date (DED):	1993/05/04
Update Date (DUPD):	1994/02/18



Field Availability:

Code	Name	Occurrence
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RN	CAS Registry Number	3
CN	Chemical Name	1
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MF	Molecular Formula	1

Saloni Sharma 07/19/2006

FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Rohloff, John C.; Robinson, James III; Gardner, John O., Tetrahedron Lett., CODEN: TELEAY, 33(22), <1992>, 3113-3116; BABS-5654059